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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/205,658	12/03/98	RUVKUN G	00786/351004

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EXAMINER	
KAUSHAL,S	
ART UNIT	**PAPER NUMBER**
1633	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/205,658	Applicant(s) Ruvkun G
	Examiner Sumesh Kaushal	Group Art Unit 1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-25 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-25 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply w/ 1.821 Seq

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The instant application is continuation-in-part of PCT/US98/10080 filed 05/15/98, which is continuation-in-part of U.S.S.N. 08/888,534 filed 07/07/97 and U.S.S.N. 08/857, 076 filed 05/15/97.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claim Objections

The numbering of claims is not accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Duplicate claim 2 (page 218, line 15) been renumbered 3. The original claim 3 is numbered 4, the claim 4=5, 5=6, 6=7, ... 23=24, and 24=25.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification fails to provide guidance for a method for identifying a compound that modulates the expression or activity of DAF-18, DAF-18 mutant gene or DAF-18 human homologue (PTEN) gene in a cell or a transgenic nematode or mouse, by contacting a cell or administering a transgenic animal with the candidate compound, which increases or decreases the DAF-18 activity. The specification fails to provide guidance to identify a candidate compound that modulates the DAF-18 activity and is capable of treating an impaired glucose tolerance condition or obesity and longevity of a cell or organism. The specification fails to provide guidance to identify a compound capable of ameliorating or delaying an impaired glucose tolerance condition or obesity and increasing the longevity of a cell or organism by contacting a biological sample with candidate compound and assaying said sample for DAF-18, DAF-18 mutant or PTEN mediated lipid phosphatase activity. Furthermore, the specification fails to teach a method of diagnosing an impaired glucose tolerance condition or obesity and longevity in a patient by analyzing the level of PTEN expression or activity in a sample isolated from the patient. The specification also fails to provide guidance for ameliorating or delaying the onset of an impaired glucose tolerance condition or obesity and increasing longevity in a patient by administering a therapeutically effective amount of a compound

that modulates the PTEN expression or activity. In addition the specification fails to provide guidance to make and use a transgenic mouse or a nematode encoding a mammalian PTEN polypeptide, wherein the animal also carries a mutation in a DAF-18 gene.

The claims are drawn to a method for identifying a compound that modulates the expression or activity of DAF-18, DAF-18 mutant gene or DAF-18 human homologue (PTEN) gene in a cell or a transgenic nematode or mouse, by contacting a cell or administering a transgenic animal with the candidate compound, which increases or decreases the DAF-18 activity. The claims are also drawn to identify a candidate compound that modulates the DAF-18 activity and is capable of treating an impaired glucose tolerance condition or obesity and longevity of a cell or organism. The claims are further drawn to identify a compound capable of ameliorating or delaying an impaired glucose tolerance condition or obesity and increasing the longevity of a cell or organism by contacting a biological sample with candidate compound and assaying the sample for DAF-18, DAF-18 mutant or PTEN mediated lipid phosphatase activity. Claims are also drawn to a method of diagnosing an impaired glucose tolerance condition or obesity and longevity in a patient by analyzing the level of PTEN expression or activity in a sample isolated from the patient. Furthermore, claims are also drawn to a method of ameliorating or delaying the onset of an impaired glucose tolerance condition or obesity and increasing longevity in a patient by administering a therapeutically effective amount of a compound that modulates the PTEN expression or activity. In addition, claims are drawn to a transgenic nematode encoding a mammalian PTEN polypeptide wherein the animal carries a mutation in a DAF-18 gene.

The specification teaches a C .elegans model for the regulation and dauer larvae arrest by insulin receptor like signaling, wherein DAF-18 limits AGE-1 PI3K signals by dephosphorylating PIP3 and/or PI(3,4)P2. In the absence of AGE-1 signals loss of DAF-18 allows an alternative

source of PIP3 and/or PI(3,4)P2 to accumulate and activates AKT-1 and AKT-2, which converge with an addition al signal pathway from DAF-2 receptor, which regulates DAF-16 trasnscrptional factor that control metabolism, reproductive growth and life span (see fig-1 App. spec). The specification teaches the inactivation of DAF-18 by RNA interference (RNAi) which partially suppresses the function of DAF-2 gene in C. elegans (see page 104, lin.5). The specification also teaches the effect of muscarinic agonists and antagonists on dauer recover in DAF-7 (e13720) and DAF-2 (e1370) mut. C. elegans (see page 47, lin.22), but it fails to show the treatment of any cell or any transgenic nematode or mouse expressing DAF-18 gene, DAF-18 mutant gene or mammalian PTEN gene for the identification of compound that modulates the expression or activity DAF-18/TPEN genes. The specification teaches that the C. elegans DAF-18 and human PTEN are homologous, but the fails to provide a guidance to an assay for measuring DAF-18 and PTEN phosphatase activity in any biological sample (see page 109, lin.9). The specification articulates measuring the expression of DAF-18 and PTEN by Northern blot or Western blot analysis in biological samples, but it fails to provide guidance to specific nucleic acid probes or antibodies against DAF-18 and PTEN or how to interpret these results (see page 197, lin.5, lin.17). Furthermore, the specification fails to provide guidance to assaying DAF-18 or PTEN mediated lipid phosphatase activity because the specification fails to teach the physiological substrates and functions of PTEN protein. The claims are read in the light of specification to identify a compound making and using a transgenic mouse or a nematode, whose germ cells or somatic cells contain a transgene encoding for a DAF-18, PTEN polypeptide wherein the transgene includes a knockout mutation (see page 14, lin.2). However, the specification fails to provide guidance to make and use any transgenic nematode or a mouse expressing DAF-18 gene, DAF-18 mutant gene or the human analog PTEN gene. The specification fails to show that a genomic DNA fragment encoding the DAF-18 or human PTEN homolog is introduced in a mouse or a nematode to make the claimed transgenic animals. The state of the art at the time of filing was such that transgene expression and

the physiological results of such an expression in animals of different species could not be accurately predicted because cis elements are controlled differently by various transacting factors in the genome of different species (Well, Theriongenology 45:57-68, 1996; see page 61, par.3). Furthermore, the specification fails to describe the regulatory regions of nematode DAF-18 and mammalian PTEN gene promoters. The disclosure of the DAF-18 and PTEN genes and its promoter are considered essential because the claims are drawn to a method for the identification of a compound that is capable of modulating the expression of a DAF-18 and PTEN gene in a mutant transgenic nematode or mouse. The art at the time of filing was such that interaction among various DAF genes in C. elegans is complex (Larsan et al, Genetics 139:1567-1583, 1995; see page 1573 fig-1). The instant specification provides no correlative teachings as to the interaction and effect of human PTEN gene other DAF genes in a nematode cellular/genetic environment and its role in glucose tolerance, obesity and increased longevity. Thus, without guidance not provided in the specification and considering the state of art, the skilled artisan at the time of filing would be lacking a reasonable expectation of success without undue experimentation to identify a compound that modulates the expression or activity of DAF-18 and TPEN genes in a cell or a transgenic nematode or mouse, and by assaying the DAF-18 and/or TPEN-mediated lipid phosphatase activity in a biological sample.

The specification indicates insulin signaling pathway can regulate dauer arrest from nervous system and may regulate aging from nervous system in mammals (see page 102, lin 20, App. Spec.). Although, longevity and diapause control is unique to C. elegans it is also an essential feature of many vertebrates or in vertebrates and the DAF-2 signaling is analogous to mammalian longevity increase associated caloric restriction (see page 103, lin 9, lin 16, App. Spec.). However, the specification fails to show that any DAF-gene is associated with the onset of impaired glucose tolerance, obesity and longevity in other animals, especially mammals. The state of the art at the time of filing was such that various factors governs the development of impaired glucose intolerance

or obesity. The mechanism underlying the development of obesity are complex and are not well understood. Obesity is a complex phenotype which is not only the result of genetic variations but is also the out come of personal behavioral and life style (Lonnqvist et al Nat. Med. 1(9):950-953, 1995, see page 951 col.1 para.1 line 1). Furthermore, the development of impaired glucose intolerance involves both hyperlipidemia and the dietary fat composition which also depends upon personal dietary habits (Zeman et al, Atherosclerosis, 134(1-2):318, 1997). Moreover, without clear correlation that DAF-18 and PTEN results in impaired glucose tolerance, obesity or increased longevity, there is no enablement for the claimed method of identifying compounds. The instant specification provides no guidance to achieve the modulation of human PTEN gene in a nematode which leads to impaired glucose tolerance, obesity and increased longevity. The therapeutic use of a compound that modulate longevity in C.elegans is not enabled for human patients because there are considerable evolutionary and environment differences between humans and C. elegans. The state of the art at the time of filing was such that when food is scarce, a reversible arrest of development is triggered in C. elegans leading to the development of metabolically less active dauer larval stage which exhibit a marked increase in longevity that is also affected by the temperature (Kimura et al, Science 277: 942-946, 1997; see page 942 col.1, par.1. Larsan et al, Genetics 139:1567-1583, 1995; see page 1577, table-4) However, the effect of caloric restriction on aging in humans is more complex because the process of ageing in humans is not only governed by various etiological factors but is also influenced by the industrialized world, modern hygiene and health care facilities (Austad, Neurobiology of Ageing 16(5):851-852, 1995, see page 851 col.2 par.3). On the other hand role of PTEN and its interaction with other DAF human homologs is not know in the art. Neither the specification nor the art at the time of filing, teaches that DAF-18 human homolog PTEN is involved in the regulation of longevity in human and nematodes. Furthermore, specification fails to show that a genomic DNA fragment encoding the human PTEN homolog could rescue the inherent defects of DAF-18 (e1375) mutant alleles in C. elegans. Thus, without guidance not

provided in the specification and considering the state of art, the skilled artisan at the time of filing would be lacking a reasonable expectation of success identifying agents for the treatment of impaired glucose intolerance, obesity and increasing longevity using the identified compound, without an undue amount of experimentation for the breadth of the claims.

Conclusion

Claims 1-25 are free of prior art. The art at the time of filing did not tech or suggest a method for the identification of compound that modulates the expression or activity of DAF-18, DAF-18 mutant or human PTEN genes, wherein the compound is capable of treating impaired glucose tolerance condition, obesity or capable of increasing the longevity in a cell, organism or a patient.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM . If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brian Stanton Ph.D. can be reached on (703) 308-2801. The fax phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

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